

# **Exhibit A**

A088 Subpoena in a Civil Case

Issued by the  
**United States District Court**  
 SOUTHERN DISTRICT OF OHIO

IN RE: '318 PATENT INFRINGEMENT  
 LITIGATION

**SUBPOENA IN A CIVIL CASE**

Case Number:<sup>1</sup> C.A. No. 05-356-KAJ (consolidated)  
 (District of Delaware)

TO: Roxane Laboratories, Inc.  
 1809 Wilson Road  
 Columbus, Ohio 43228

- ☐ YOU ARE COMMANDED to appear in the United States District court at the place, date, and time specified below to testify in the above case.

PLACE OF TESTIMONY

COURTROOM

DATE AND TIME

- ☒ YOU ARE COMMANDED to appear at the place, date, and time specified below to testify at the taking of a deposition in the above case. Please See Schedule A Attached

PLACE OF DEPOSITION Recording Method: By stenographer and videotape

McGinnis &amp; Associates, 175 South Third Street, Suite 540, Columbus, OH, 43215

DATE AND TIME

May 5, 2006 at 10:00 a.m.

- ☒ YOU ARE COMMANDED to produce and permit inspection and copying of the following documents or objects at the place, date, and time specified below (list documents or objects): Please See Schedule B Attached

PLACE

McGinnis &amp; Associates, 175 South Third Street, Suite 540, Columbus, OH, 43215

DATE AND TIME

April 28, 2006 at 10:00 a.m.

- ☐ YOU ARE COMMANDED to permit inspection of the following premises at the date and time specified below.

PREMISES

DATE AND TIME

Any organization not a party to this suit that is subpoenaed for the taking of a deposition shall designate one or more officers, directors, or managing agents, or other persons who consent to testify on its behalf, and may set forth, for each person designated, the matters on which the person will testify. Federal Rules of Civil Procedure, 30(b)(6).

ISSUING OFFICER'S SIGNATURE AND TITLE (INDICATE IF ATTORNEY FOR PLAINTIFF OR DEFENDANT)  
 Attorney for Plaintiffs Janssen Pharmaceutica N.V., Janssen L.P., and Synaptech, Inc.

DATE AND TIME  
 April 4, 2006

ISSUING OFFICER'S NAME, ADDRESS AND PHONE NUMBER

Tiffany Geyer Lydon, Esq.  
 222 Delaware Avenue, 17th Floor  
 Wilmington, DE 19899  
 Tel: 302-654-1888

(See Rule 45, Federal Rules of Civil Procedure, Parts C&D on next page)

<sup>1</sup> If action is pending in district other than district of issuance, state district under case number.

A088 Subpoena in a Civil Case

**PROOF OF SERVICE**

DATE	PLACE
SERVED	
SERVED ON (PRINT NAME)	MANNER OF SERVICE
SERVED BY (PRINT NAME)	TITLE

**DECLARATION OF SERVER**

I declare under penalty of perjury under the laws of the United States of America that the foregoing information contained in the Proof of Service is true and correct.

Executed on \_\_\_\_\_ DATE \_\_\_\_\_ SIGNATURE OF SERVER \_\_\_\_\_

ADDRESS OF SERVER \_\_\_\_\_

**Rule 45, Federal Rules of Civil Procedure, Parts C&D****(c) PROTECTION OF PERSONS SUBJECT TO SUBPOENAS.**

(1) A party or an attorney responsible for the issuance and service of a subpoena shall take reasonable steps to avoid imposing undue burden or expense on a person subject to that subpoena. The court on behalf of which the subpoena was issued shall enforce this duty and impose upon the party or attorney in breach of this duty an appropriate sanction which may include, but is not limited to, lost earnings and reasonable attorney's fee.

(2)(A) A person commanded to produce and permit inspection and copying of designated books, papers, documents or tangible things, or inspection of premises need not appear in person at the place of production or inspection unless commanded to appear for deposition, hearing or trial.

(2)(B) Subject to paragraph (d)(2) of this rule, a person commanded to produce and permit inspection and copying may, within 14 days after service of subpoena or before the time specified for compliance if such time is less than 14 days after service, serve upon the party or attorney designated in the subpoena written objection to inspection or copying of any or all of the designated materials or of the premises. If objection is made, the party serving the subpoena shall not be entitled to inspect and copy materials or inspect the premises except pursuant to an order of the court by which the subpoena was issued. If objection has been made, the party serving the subpoena may, upon notice to the person commanded to produce, move at any time for an order to compel the production. Such an order to compel production shall protect any person who is not a party or an officer of a party from significant expense resulting from the inspection and copying commanded.

(3) (A) On timely motion, the court by which a subpoena was issued shall quash or modify the subpoena if it

- (i) fails to allow reasonable time for compliance,
- (ii) requires a person who is not a party or an officer of a party to travel to a place more than 100 miles from the place where that person resides, is employed or regularly transacts business in person, except that, subject to

the provisions of clause (c)(3)(B)(iii) of this rule, such a person may in order to attend trial be commanded to travel from any such place within the state in which the trial is held, or

(iii) requires disclosure of privileged or other protected matter and no exception or waiver applies, or

(iv) subjects a person to undue burden

(3)(B) If a subpoena

(i) requires disclosure of a trade secret or other confidential research, development, or commercial information, or

(ii) requires disclosure of an unretained expert's opinion or information not describing specific events or occurrences in dispute and resulting from the expert's study made not at the request of any party, or

(iii) requires a person who is not a party or an officer of a party to incur substantial expense to travel more than 100 miles to attend trial, the court may, to protect a person subject to or affected by the subpoena, quash or modify the subpoena, or, if the party in who behalf the subpoena is issued shows a substantial need for the testimony or material that cannot be otherwise met without undue hardship and assures that the person to whom the subpoena is addressed will be reasonably compensated, the court may order appearance or production only upon specified conditions.

**(d) DUTIES IN RESPONDING TO SUBPOENA.**

(1) A person responding to a subpoena to produce documents shall produce them as they are kept in the usual course of business or shall organize and label them to correspond with the categories in the demand.

(2) When information subject to a subpoena is withheld on a claim that it is privileged or subject to protection as trial preparation materials, the claim shall be made expressly and shall be supported by a description of the nature of the documents, communications, or things not produced that is sufficient to enable the demanding party to contest the claim.

**SCHEDULE A**

**DEFINITIONS**

1. “Synaptech” shall mean Plaintiff Synaptech, Inc., Synaptec, Inc., and all of Synaptech, Inc., its corporate parents, corporate predecessors and past or present subsidiaries, affiliates, divisions, departments, officers, directors, principals, agents and employees including without limitation Bonnie M. Davis, M.D. and Synaptec, Inc.

2. “Dr. Bonnie Davis” refers to Bonnie M. Davis, M.D., holder of United States Patent No. 4,663,318.

3. “You,” “your,” “yours,” or “Roxane” shall mean Roxane Laboratories, Inc. and all of Roxane Laboratories, Inc.’s corporate parents, including but not limited to Boehringer Ingelheim KG, corporate predecessors and past or present subsidiaries, affiliates, divisions, departments, officers, directors, principals, agents, employees and any individuals or entities that at any time have acted or purported to act on behalf of Roxane Laboratories, Inc. or its successors.

4. “Communication” and “communications” mean any contact, transmission, or exchange of information between two or more persons, verbally or in writing or by any other means.

5. “Concerning” means relating to, referring to, regarding, describing, being evidence of, constituting, memorializing, or reflecting in any way.

6. “Document” means the complete original (or complete copy where the original is unavailable) and each non-identical copy (where different from the original because of notes made on the copy or otherwise) of any writing or record, including but not limited to all written, typewritten, handwritten, printed or graphic matter of any kind or

nature, however produced or reproduced, any form of collected data for use with electronic data processing equipment, and any mechanical or electronic visual or sound recordings, including, without limitation, all tapes and discs, now or formerly in your possession, custody or control, including all documents as defined in the broadest sense permitted by the Federal Rules of Civil Procedure. The term “document” includes, but is not limited to, e-mails, invoices, purchase orders, checks, receipts, letters and other correspondence, offers, contracts, agreements, bids, proposals, licenses, permits, reports to government agencies, ledgers, accounts receivable, accounts payable, account statements, financial statements, monthly reports, other reports, minutes of meetings, sales estimates, sales reports, memoranda, notes, calendar or diary entries, agendas, bulletins, graphs, charts, maps, photographs, drawings, surveys, data, price lists, summaries, telegrams, teletypes, computer printouts, magnetic tapes, discs, microfilm, and microfiche.

7. “Person” and “persons” mean any natural person and any business, legal, corporate, or governmental entity, association, or organization.

8. “Alzheimer’s Disease” means any diagnosis, illness, or ailment described as being of the Alzheimer’s type, including without limitation Senile Dementia of the Alzheimer’s Type, and/or Alzheimer’s Dementia.

9. “318 patent” means United States Patent No. 4,663,318 attached hereto as Exhibit 1.

10. “Galantamine” includes without limitation galantamine, galanthamine, and any salt of galatamine, such as galantamine hydrobromide.

11. In these Requests, the present tense includes the past and future tenses, the connectives “and” and “or” shall be construed either disjunctively or conjunctively as

necessary to bring within the scope of the Request all responses that might otherwise be construed to be outside of its scope, the singular shall include the plural and vice versa, “all” shall include “any” and vice versa, and “each” shall include “every” and vice versa, all to the end that each Request shall be construed to cover the broadest scope of information.

### **TOPICS**

1. The names and responsibilities of all persons involved in any evaluation, consideration, or discussion to license the ‘318 patent or to develop or market a product within its claims, and the file and contribution of such person in each such evaluation, consideration or discussion.

2. The names and responsibilities of all persons involved in any evaluation, consideration, or discussion of galantamine as a treatment for Alzheimer’s Disease, and the file and contribution of such person in each such evaluation, consideration or discussion.

3. All negotiations or communication with Synaptech or Dr. Bonnie Davis regarding the ‘318 patent.

4. All negotiations or communication with Synaptech or Dr. Bonnie Davis regarding galantamine as a treatment for Alzheimer’s Disease.

5. The November 8, 1989, letter from Prof. E. Muller, Department of Pharmacology, Boehringer Ingelheim KG, attached hereto as Exhibit 2 including without limitation the meaning of, basis for, and any evaluation or analysis concerning the statements set forth in the letter that “based on our extensive preclinical research data available to us, it is our feeling that this compound, while interesting from the point of view of its

mechanism of action (acetylcholinesterase inhibitor), does not have the biochemical and pharmacological profile which we consider essential for its potential use in the treatment of Alzheimer's disease."

6. The proposal by Waldheim Pharmazeutika reported in Exhibit 2 "to develop nivalin (galanthamine) for the indication Alzheimer's disease," including without limitation any discussion, evaluation, or consideration of that proposal.

7. The Confidentiality Agreement dated November 10, 1989, attached hereto as Exhibit 3.

8. The April 26, 2005, letter from Randall S. Wilson, Vice President Scientific Affairs, attached hereto as Exhibit 4, including without limitation the meaning of, basis for, and any evaluation or analysis concerning the statement set forth in the letter that "Roxane is seeking approval to market its proposed product after expiration of U.S. Patent No. 4,663,318 on December 12, 2008 (including a patent term extension under 35 USC §156)."

9. Any and all patent certifications made by Roxane to the FDA concerning the '318 patent.

10. All communications or discussions between Roxane and any other person regarding the '318 patent.

### **SCHEDULE B**

Pursuant to Rule 45 of the Federal Rules of Civil Procedure, Plaintiffs Janssen Pharmaceutica N.V., Janssen, L.P., and Synaptech, Inc. hereby propound this subpoena on Roxane Laboratories, Inc. This subpoena calls for you to produce the documents described under the heading “Requests for Production of Documents” below, in accordance with the following “Definitions” and “Instructions.”

### **DEFINITIONS**

Notwithstanding any definition set forth below, each word, term, or phrase used in these Requests is intended to have the broadest meaning permitted under the Federal Rules of Civil Procedure. The following definitions and rules on construction apply to the Requests:

1. “Synaptech” shall mean Plaintiff Synaptech, Inc., Synaptec, Inc., and all of Synaptech, Inc., its corporate parents, corporate predecessors and past or present subsidiaries, affiliates, divisions, departments, officers, directors, principals, agents and employees including but not limited to Bonnie M. Davis, M.D.
2. “Dr. Bonnie Davis” refers to Bonnie M. Davis, M.D., holder of United States Patent No. 4,663,318.
3. “You,” “your,” “yours,” or “Roxane” shall mean Roxane Laboratories, Inc. and all of Roxane Laboratories, Inc.’s corporate parents, including but not limited to Boehringer Ingelheim KG, corporate predecessors and past or present subsidiaries, affiliates, divisions, departments, officers, directors, principals, agents, employees and any individuals

or entities that at any time have acted or purported to act on behalf of Roxane Laboratories, Inc. or its successors.

4. “Communication” and “communications” mean any contact, transmission, or exchange of information between two or more persons, verbally or in writing or by any other means.

5. “Concerning” means relating to, referring to, regarding, describing, being evidence of, constituting, memorializing, or reflecting in any way.

6. “Document” means the complete original (or complete copy where the original is unavailable) and each non-identical copy (where different from the original because of notes made on the copy or otherwise) of any writing or record, including but not limited to all written, typewritten, handwritten, printed or graphic matter of any kind or nature, however produced or reproduced, any form of collected data for use with electronic data processing equipment, and any mechanical or electronic visual or sound recordings, including, without limitation, all tapes and discs, now or formerly in your possession, custody or control, including all documents as defined in the broadest sense permitted by the Federal Rules of Civil Procedure. The term “document” includes, but is not limited to, e-mails, invoices, purchase orders, checks, receipts, letters and other correspondence, offers, contracts, agreements, bids, proposals, licenses, permits, reports to government agencies, ledgers, accounts receivable, accounts payable, account statements, financial statements, monthly reports, other reports, minutes of meetings, sales estimates, sales reports, memoranda, notes, calendar or diary entries, agendas, bulletins, graphs, charts, maps, photographs, drawings, surveys, data, price lists, summaries, telegrams, teletypes, computer printouts, magnetic tapes, discs, microfilm, and microfiche.

7. “Person” and “persons” mean any natural person and any business, legal, corporate, or governmental entity, association, or organization.

8. “Alzheimer’s Disease” means any diagnosis, illness, or ailment described as being of the Alzheimer’s type, including without limitation Senile Dementia of the Alzheimer’s Type, and/or Alzheimer’s Dementia.

9. “318 patent” means United States Patent No. 4,663,318 attached hereto as Exhibit 1.

10. “Galantamine” includes without limitation galantamine, galanthamine, and any salt of galatamine, such as galantamine hydrobromide.

11. In these Requests, the present tense includes the past and future tenses, the connectives “and” and “or” shall be construed either disjunctively or conjunctively as necessary to bring within the scope of the Request all responses that might otherwise be construed to be outside of its scope, the singular shall include the plural and vice versa, “all” shall include “any” and vice versa, and “each” shall include “every” and vice versa, all to the end that each Request shall be construed to cover the broadest scope of information.

### **INSTRUCTIONS**

1. The response to each Request shall include all documents within your possession, custody, or control. The phrase “possession, custody, or control” means a document in your physical custody; or, that you own in whole or in part; or, have a right by contract, statute or otherwise to use, inspect, examine or copy on any terms; have an understanding, express or implied, that you may use, inspect, examine or copy on any terms; or you have, as a practical matter, the ability to use, inspect, examine or copy such document.

2. If any document or tangible thing that would have been responsive to the Requests below has been destroyed or is no longer in your possession, custody or control, you shall serve upon the undersigned counsel for the Plaintiff a written list that (i) identifies each such document by date, author or preparer, and addressee(s); and (ii) states the date of, and identity of the person responsible for, its destruction, loss, transfer, or other action by which the document or tangible thing left your possession, custody or control.

3. The response to each Request shall state, with respect to each item or category, that inspection and related activities will be permitted as requested, unless the Request is objected to, in which event the reasons for objection shall be stated. If objection is made to part of an item or category, the part shall be specified. Any such objection shall not extend the time within which you must otherwise answer or respond to a Request to which no specific objection has been made.

4. If you contend that an otherwise discoverable document would be excludable from production, state the reasons for such objection or grounds for exclusion and identify each person having knowledge of the factual basis, if any, on which the objection or ground is asserted.

5. If any document that would have been responsive to any of the Requests below is not produced because of a claim of privilege or immunity, you shall serve upon the undersigned counsel for the Plaintiff a written list that (i) identifies each such document by date, author or preparer, and addressee(s); (ii) identifies the name and position of each person to whom a copy was furnished, and each person to whom the original or a copy was shown; (iii) states the general subject matter of each document; (iv) identifies the Request to which the withheld document is responsive; and (v) states the ground on which each document is asserted to be privileged or immune from disclosure. Any attachment to an allegedly privileged or immune document shall be produced unless you contend that the attachment is also privileged or immune, in which case the information specified in the previous sentence shall be separately provided for each such attachment.

6. If there is any question as to the meaning of any part of these Requests, or an issue as to whether production of responsive documents would impose an undue burden, counsel for the Plaintiff should be contacted promptly.

7. You may produce legible, complete, and exact copies of the original documents, provided that the originals be made available for inspection upon request by counsel for the Plaintiff.

8. You are requested to respond in writing to the following Requests, and produce the requested documents for inspection and copying, at the time, date, and location set forth in the subpoena.

**REQUESTS FOR PRODUCTION OF DOCUMENTS**

1. All documents concerning any evaluation, analysis, consideration or discussion to license the '318 patent, including without limitation any evaluation analysis, consideration or discussion by Boehringer Ingelheim KG.

2. All documents concerning any evaluation, analysis, consideration, or discussion concerning the development of a product containing galantamine for the treatment of Alzheimer's disease, including without limitation any evaluation, analysis, consideration, or discussion by Boehringer Ingelheim KG.

3. All documents concerning communications or discussions between you and Synaptech or Dr. Bonnie Davis regarding the '318 patent.

4. All documents concerning communication between you and Synaptech or Dr. Bonnie Davis regarding galantamine as a treatment for Alzheimer's Disease.

5. All documents concerning the November 8, 1989, letter from Professor E. Muller, Department of Pharmacology, attached hereto as Exhibit 2, including without limitation all documents concerning the meaning of, basis for, and any evaluation or analysis concerning the statement set forth in the letter that "it is our feeling that this compound, while interesting from the point of view of its mechanism of action (acetylcholinesterase inhibitor), does not have the biochemical and pharmacological profile which we consider essential for its potential use in the treatment of Alzheimer's disease."

6. All documents concerning the proposal by Waldheim Pharmazeutika reported in Exhibit 2 "to develop nivalin (galanthamine) for the indication Alzheimer's disease," including without limitation all documents concerning any discussion, evaluation, analysis, or consideration of that proposal."

7. All documents concerning the Confidentiality Agreement dated November 10, 1989, attached hereto as Exhibit 3.

8. All documents concerning the patent certifications made by Roxane to the FDA concerning the '318 patent.

9. All documents concerning any communication or discussion between you and any person concerning the '318 patent.

## **EXHIBIT 1**



**United States Patent** [19]

**Davis**

[11] **Patent Number:** **4,663,318**

[45] **Date of Patent:** **May 5, 1987**

[54] **METHOD OF TREATING ALZHEIMER'S DISEASE**

[76] **Inventor:** **Bonnie Davis, 17 Seacrest Dr.,  
Huntington, N.Y. 11743**

[21] **Appl. No.:** **819,141**

[22] **Filed:** **Jan. 15, 1986**

[51] **Int. Cl.:** ..... **A61K 31/55**

[52] **U.S. Cl.:** ..... **514/215**

[58] **Field of Search** ..... **514/215**

[56] **References Cited  
PUBLICATIONS**

Chem. Abst. (81)-72615z (1974).  
Chem. Abst. (86)-115157z (1977).

Horshenson et al. J. Med. Chem. vol. 29, No. 7, 7/86,  
pp. 1125-1130.

Kendall et al., J. Chem. & Hospital Pharmacol., (1985)  
10-327-330.

S. Chaplygina et al., J. of Highest Nervous Activity vol.  
XXIV 1976 Issue 5, pp. 1-4.

Krause, J. of Highest Nervous Activity, vol. XXII,  
1974, Issue 4.

*Primary Examiner*—Stanley J. Friedman  
*Attorney, Agent, or Firm*—Ladas & Parry

[57] **ABSTRACT**

Alzheimer's disease may be treated with galanthamine.

**7 Claims, No Drawings**

4,663,318

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## METHOD OF TREATING ALZHEIMER'S DISEASE

### GENERAL FIELD OF THE INVENTION

The present invention relates to a novel method of treating Alzheimer's disease and more particularly to a treatment using galanthamine.

### BACKGROUND ART

Galanthamine and acid addition salts thereof have, for many years, been known to have anticholinesterase properties. Cozanitis in *Anaesthesia* 29 163-8 (1974) describes the effect of galanthamine hydrobromide on plasma cortisol of patients receiving relaxant anaesthesia and Cozanitis et al in *Acta Anaesth. Scand.* 24:166-168 (1980) describe the effect of galanthamine on plasma ACTH values during anaesthesia. These studies showed an increase in both plasma cortisol and plasma ACTH when galanthamine was administered to patients together with atropine.

Il'yuchenok et al (Chemical Abstracts 70 36296K) describe the appearance of  $\theta$ -rhythm on an electroencephalogram when galanthamine is administered intravenously to rabbits.

Increase in short-term memory in dogs by use of galanthamine is described by Krauz in Chemical Abstracts 81 72615Z.

The antagonistic effect of galanthamine to scopalamine-induced amnesia in rats is described by Chaplygina et al in Chemical Abstracts 86 115157Z, and in *Zhurnal Vyshei Nervnoi Deiatelnosti imeni P. Pavlova (MOSKVA)* 26:1091-1093, 1976.

Alzheimer's disease, presenile dementia, causes much distress not only to those suffering from the disease, but also those who are close to them. The custodial care of advanced victims of the disease is a tremendous expense to society. At present, there is no effective means of improving the functional status of persons with the disease.

It is an object of the present invention to improve the cognitive function of patients with Alzheimer's disease.

### SUMMARY OF THE INVENTION

A method for treating Alzheimer's disease and related dementias which comprises administering to mammals, including humans, an effective Alzheimer's disease cognitively-enhancing amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof. A radioactively-labelled form of the molecule may also serve as a diagnostic test for Alzheimer's disease.

### DETAILED DESCRIPTION OF THE INVENTION

Galanthamine can be administered in any convenient chemical or physical form. For example, it may be administered as its hydrobromide, hydrochloride, methylsulfate or methiodide.

Galanthamine or its pharmaceutically-acceptable acid addition salts may be administered to a patient suffering from Alzheimer's disease orally or by subcutaneous or intravenous, injection, or intracerebroventricularly by means of an implanted reservoir. It may be necessary to begin at lower doses than are ultimately effective.

Galanthamine and its acid addition salts form crystals. They are in general only sparingly soluble in water

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at room temperature and so injectible compositions are normally in the form of an aqueous suspension. If necessary, pharmaceutically-acceptable suspension aids may be employed. Typically, such a suspension will be employed at a concentration of 1-50 mg/ml more commonly 5-40 mg/ml, for example, 5-30 mg/ml or 10-40 mg/ml, typically 20-30 mg/ml of galanthamine. Typical dosage rates when administering galanthamine by injection are in the range 5-1,000 mg per day depending upon the patient. For example, divided doses in the range 0.5-5 mg/kg body weight per day may prove useful. Typically, one might administer a dosage of 50-300 mg per day to a patient of a body weight of 40-100 kg, although in appropriate cases such dosages may prove useful for patients having a body weight outside this range. In other cases, dosages as low as 10 mg and as high as 500 mg may be appropriate for persons in this body weight range.

Galanthamine or its pharmaceutically-acceptable acid addition salts may also be administered orally, for example, as an aqueous suspension or a solution in aqueous ethanol or as a solid such as a tablet or capsule. Suspensions or solutions for oral administration are typically of about the same concentration as those used for injections. However, it may be desirable when administering the drug orally to use a higher dosage rate than when administering it by injection. For example, dosages up to 2000 mg per day may be used, such as dosages in the range 100-600 mg per day. In preparing such tablets or capsules, standard tablet or capsulemaking techniques may be employed. The dosage rate of galanthamine or its pharmaceutically-acceptable salt will normally be in the same range as for oral administration of a liquid. If desired, a pharmaceutically-acceptable carrier such as starch or lactose may be used in preparing galanthamine tablets. Capsules may be prepared using soft galatine as the encapsulating agent. If desired, such capsules may be in the form of sustained release capsules wherein the main capsule contains microcapsules of galanthamine which release the contents over a period of several hours thereby maintaining a constant level of galanthamine in the patient's blood stream.

The following test provides a good animal model for Alzheimer's disease in humans: A selective lesion is placed in a subcortical nucleus (nucleus basalis of Meynert) with a resultant cortical cholinergic deficiency, similar in magnitude to that seen in early to moderate stage Alzheimer's disease. Numerous behavioral deficits, including the inability to learn and retain new information, characterizes this lesion. Drugs that can normalize these abnormalities would have a reasonable expectation of efficacy in Alzheimer's disease. Haroutunian, V, Kanof P, Davis, KL: Pharmacological alleviations of cholinergic-lesion-induced memory defects in rats. *Life Sciences* 37:945-952, 1985.

The following specific formulations may find use in treatment of Alzheimer's disease:

Tablets or capsules containing 5, 10 and 25 mg galanthamine hydrobromide to be taken four times a day, or a sustained-release preparation delivering an equivalent daily dose.

Parenteral solution containing 5 mg/ml.

Liquid formulation for oral administration available in 5 mg/5 ml and 25 mg/5 ml concentration.

There have been reports that galanthamine can cause cardiac arrhythmias. In such cases, it may be desirable to

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administer galanthamine in conjunction with another drug such as propanthelinbromide to control such arrhythmias.

I claim:

1. A method of treating Alzheimer's disease and related dementias which comprises administering to a patient suffering from such a disease a therapeutically effective amount of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.

2. A method according to claim 1, wherein the administration is parenteral at a daily dosage of 5-1,000 mg of galanthamine or a pharmaceutically-acceptable acid addition salt thereof.

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3. A method according to claim 2, wherein said dosage rate is 50-300 mg per day.

4. A method according to claim 1, wherein said administration is oral and is in the range 10-2000 mg per day.

5. A method according to claim 4, wherein said dosage rate of 100-600 mg per day.

6. A method according to claim 1, wherein galanthamine is administered at a dosage rate of 0.1 to 4 mg/kg body weight of a patient, parenterally.

7. A method according to claim 1, wherein galanthamine is administered intracerebroventricularly via an implanted reservoir at a dosage rate of 0.01 to 5.0 mg/kg day.

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## **EXHIBIT 2**

# Boehringer Ingelheim



Boehringer Ingelheim KG · 6507 Ingelheim am Rhein

Boehringer Ingelheim KG

Prof. Dr. P. Placheta  
Bender & Co. Ges.m.b.H.  
Dr.-Boehringer-Gasse 5 - 11  
A-1120 Wien

Ihr Zeichen

Ihre Nachricht vom

Unser Zeichen

Dr. Mü-ra

Telefon-Durchwahl

06132-77-4194

6507 Ingelheim am Rhein,

den November 8., 1989

Dear Prof. Placheta,

we have given serious consideration to the proposal of Waldheim Pharmazeutika to develop Nivalin (galanthamine) for the indication Alzheimer's disease. Based on the extensive preclinical research data available to us, it is our feeling that this compound, while interesting from the point of view of its mechanism of action (acetylcholinesterase inhibitor), does not have the biochemical and pharmacological profile which we consider essential for its potential use in the treatment of Alzheimer's disease. The limited clinical data (pilot study by Michael Rainer) are not very convincing.

Furthermore, Dr. Bonnie Davis has already applied for a patent to use galanthamine in AD-patients in the US and several other countries. To my knowledge, this patent has been granted and Waldheim Pharmazeutika is well aware of this.

We would, therefore, not recommend that Boehringer should get involved in the development of Nivalin for the treatment of Alzheimer's disease.

With best regards

BOEHRINGER INGELHEIM KG  
ppa.

i. v.

Dr. M. Herschel  
(Dept. of Medicine)

*Müller*  
Prof. E. Müller  
(Dept. of Pharmacology)

cc.: Prof. Jennewein  
Dr. Bachtler  
Dr. Heil

Dr. Bonnie Davis  
(Mount Sinai Medical Center, N.Y.)

Geschäftsführung: Hansjörg Fanger, Vorsitzender · Werner Hoffmann · Dr. Herbert Johann · Dr. Eberhard Kutter · Dr. Meinrad Roßmann  
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Boehringer Ingelheim AG  
Fax 77-3080

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Dresdner Bank AG, Mainz 249 569 700 (BLZ 550 830 65)  
Landeszentralbank Mainz 55007 367 (BLZ 550 000 00)

Kreissparkasse Bingen 1008 300 (BLZ 552 500 10)  
Postsparkasse Frankfurt/Main 1053-602 (BLZ 500 100 00)

051/46

## **EXHIBIT 3**

16 NOV. '89 09:43 BI KG PHARMKOLOGIE 8888

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## IDENTIALITY AGREEMENT

IN WITNESS WHEREOF, this agreement, made this 10<sup>th</sup> day of November, 1989, by and between Dr. B. Davis (hereinafter referred to as "bjm"), and ~~Boehringer Ingelheim Corporation, of Ridgefield, Connecticut and West Germany, (hereinafter referred to as "BI")~~

~~\* International Subst \* KG~~  
WITNESSETH

Whereas, bjm possesses certain confidential trade secret information, data and know-how relating to products for the treatment of Alzheimer's disease and related dementias ("product"); and

Whereas, BI wishes to receive said confidential trade secret information, data and know-how for the purpose of evaluating same to determine its commercial interest therein; and

Whereas, bjm is agreeable to providing BI with said information upon the terms and conditions as stated hereinafter,

Now, therefore, in consideration of the foregoing mutual premises and mutual covenants recited herein, the parties hereto agree as follows:

1. "Confidential information", as used herein, means any and all information relating to the product furnished by bjm to BI, either directly or indirectly, with the exception only of the following:

(a) information that as of the date of receipt by BI is publicly available or subsequently becomes so without fault on the part of BI;

(b) information that at the time of receipt by BI was known to it from its own sources;

(c) information that at any time is received in good faith by BI from a third party that was lawfully in possession of the same and had the right to disclose the same; and

(d) information that the parties hereto mutually agree to release from the terms of this agreement.

2. Promptly following execution of this Agreement, bjm shall provide BI with such information that bjm has in its possession relating to the product as may be necessary and sufficient for BI to determine its commercial interest therein.

3. BI agrees to receive and maintain in confidence all Confidential information to no one other than its officers and employees or governmental regulatory officials who are directly concerned with its evaluation, and shall take all reasonable precautions to prevent the disclosure of Confidential information to any unauthorized person, firm, or company. Upon disclosing Confidential information to its officers and employees or governmental regulatory officials, BI shall advise said officers and employees of the confidential nature thereof, and shall use

reasonable efforts to prevent the unauthorized disclosure of such information by such officers and employees.

4. BI agrees not to use Confidential Information for any purpose other than the evaluation referred to in Paragraph 2 above without first obtaining the express written consent of bjm to do so or except pursuant to a further contractual arrangement between BI and bjm.

5. In the event BI does not wish to pursue product following its review, BI, at bjm's request, shall return all confidential information to bjm.

6. It is understood and agreed that the obligations of BI under this agreement shall continue for a period of ten (10) years from the date hereof, at the expiration of which period such obligations shall terminate.

7. It is understood that the obligations of BI under this agreement apply also to all other affiliates of BI.

IN WITNESS WHEREOF, each party hereto has caused this instrument to be executed, in duplicate, by its duly authorized representative as of the date first above written.

<sup>KG</sup>  
Boehringer Ingelheim Corporation

~~Intergene Inc.~~

By *Franklin Müller*  
Title PPA I.V.

Date Nov. 13, 1989

By *Bonnie M. Davis*  
Bonnie M. Davis, M.D.

Date Nov. 10, 1989

## **EXHIBIT 4**



Boehringer Ingelheim  
Roxane Laboratories

April 26, 2005

Attn: William C Weldon  
Chairman, Board of Directors & Chief Executive Officer  
Johnson & Johnson  
1 Johnson & Johnson Plaza  
New Brunswick, NJ 08933

Re: Patent Notice Pursuant to § 505(j)(2)(B)(ii) [21 USC § 355(j)(2)(B)(ii)]

Dear Mr. Weldon:

Roxane Laboratories, Inc., hereby notifies you that it has submitted to the FDA an abbreviated new drug application (ANDA) seeking approval for galantamine hydrobromide in a tablet formulation for treatment of Alzheimer's disease, and that the ANDA contains a Paragraph IV certification that U.S. Patent Nos. 6,099,863 ("the '863 patent") and 6,358,527 ("the '527 patent"), both of which expire on June 6, 2017, will not be infringed. The detailed statement of the factual and legal basis as to why the aforementioned Orange Book patents are not infringed is set forth below. It will be understood that the following statement may not be exhaustive of the grounds on which the patents are not infringed, invalid and/or unenforceable, and that Roxane Laboratories expressly reserves the right to assert additional grounds in any litigation commenced against it asserting patent infringement pursuant to 35 U.S.C. § 271.

**I. Roxane's Proposed Product**

Roxane's proposed galantamine product is a tablet formulation comprising galantamine hydrobromide. Roxane's proposed formulation utilizes galantamine hydrobromide as the active ingredient, in combination with a mixture of lactose anhydrous (50-70% w/w) as a diluent and microcrystalline cellulose (15-45% w/w) as a diluent. Roxane will seek to market its galantamine tablet formulation for use in the treatment of Alzheimer's disease.

**II. The '863 Patent**

The '863 patent contains ten (10) claims wherein claim 1 is the only independent claim. The '863 patent is scheduled to expire on June 6, 2017.

Independent claim 1 of the '863 patent recites the following:

1. A tablet comprising as an active ingredient a therapeutically effective amount of galanthamine hydrobromide (1:1) and a pharmaceutically acceptable carrier, wherein said carrier comprises a spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25) as a diluent, and an insoluble or poorly soluble cross-linked polymer disintegrant.



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Roxane's formulation utilizes galantamine hydrobromide as the active ingredient, in combination with a mixture of lactose *anhydrous* (50-70% w/w) as a diluent and microcrystalline cellulose (15-45% w/w) as a diluent. The '863 patent claims are limited to a spray-dried mixture of lactose *monohydrate* and microcrystalline cellulose (75:25) as a diluent. Based upon the disclosure in the '863 patent at col. 3, lines 10-35, a mixture of lactose anhydrous with microcrystalline cellulose, as is being used by Roxane, was tried but did not work according to their experiments. It was only the specific spray-dried mixture of lactose monohydrate and microcrystalline cellulose, sold commercially as Microcelac™, that provided the desired results according to the experiments conducted in the '863 patent. As such, claim 1 of the '863 patent clearly does not cover Roxane's proposed blend of lactose anhydrous with microcrystalline cellulose as the diluents in the galantamine tablet formulations, either literally or under the doctrine of equivalents.

The remaining claims 2-10 all depend from claim 1. As such, because Roxane's galantamine tablet formulation does not infringe claim 1, it cannot infringe the claims which depend therefrom as those claims contain all of the limitations of claim 1. Therefore, Roxane's galantamine tablet formulation also does not infringe claims 2-10 of the '863 patent.

### **III. The '527 Patent**

The '527 patent contains six (6) claims of which claims 1 and 6 are independent claims. The '527 patent, being a continuation of the '863 patent, is scheduled to expire on June 6, 2017.

The '527 patent has claims directed to methods of using (claims 1-5) and a method of making (claim 6) galantamine formulations which, like the '863 patent, utilize the spray-dried mixture of lactose monohydrate and microcrystalline cellulose (75:25). Accordingly, Roxane's proposed galantamine tablet formulation does not fall within the scope of the '527 patent claims for the same reasons as set forth concerning the '863 patent since claims 1-6 of the '527 patent clearly do not cover, either literally or under the doctrine of equivalents, Roxane's proposed blend of lactose *anhydrous* with microcrystalline cellulose as the diluents in the galantamine tablet formulation.

For at least the foregoing reasons, Roxane's proposed formulation will not infringe claims 1-10 of the '863 patent or claims 1-6 of the '527 patent, either literally or under the doctrine of equivalents. However, by this certification Roxane Laboratories is in no way limiting its defenses and expressly reserves the right to assert additional claims, including invalidity and unenforceability, under all relevant sections of the patent laws or other applicable laws in the United States.



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For your further reference, Roxane is seeking approval to market its proposed product after expiration of U.S. Patent No. 4,663,318 on December 12, 2008 (including a patent term extension under 35 USC §156). Therefore, Roxane will not infringe the '318 patent which will have expired.

Finally, Roxane hereby makes its offer of confidential disclosure pursuant to 21 U.S.C. §355(j)(5)(C)(i)(1)(cc). This offer of confidential access to Roxane's ANDA is specifically restricted to Janssen Pharmaceutical's ("Janssen") outside legal counsel and to one in-house counsel who does not have any responsibility for procurement of patents relating to and/or development of any galantamine products, and is for the sole and limited purpose of evaluating whether the aforementioned '863 and '527 patents will be infringed, and for no other purpose. This offer of confidential access is also subject to Janssen's agreement to (i) treat Roxane's documents and the information contained therein with the same degree of care that Janssen accords its own confidential documents, (ii) not to disclose any of Roxane's documents or the information contained therein to anyone excepting the persons identified above, and (iii) if Roxane elects to provide copies of documents to Janssen, then upon Janssen's determination on the question of infringement, to return to Roxane all of Roxane's documents and all copies thereof, and to destroy all notes, summaries or other documents concerning the information contained in Roxane's documents (excepting that the individuals identified above may retain a summary of the reasons for Janssen's determination of no infringement). If Janssen accepts this offer of confidential access, Roxane reserves the right to redact from its documents information not of relevance to the question of patent infringement.

If you have any reason to disagree with Roxane's Laboratories position, please contact Randy Wilson Vice President Scientific Affairs. He can be reached at 614-272-4799 and by telefax at 614-279-4659. In my absence, please contact Julie Economou at 614-241-4118.

Respectfully,

Randall S. Wilson  
Vice President Scientific Affairs  
Roxane Laboratories

CC: Janssen Pharmaceutical CEO Peter Miller  
Janssen Legal Department